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By LEONARD ROGERS, M.B., M.R.C.P., I.M.S.,
Officiating Professor of Pathology, Medical College, Calcutta.

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IS "MALARIAL CACHEXIA" PURELY MALARIAL?

By LEONARD ROGERS, M.D., M.R.C.P., I.M.S.,

Officiating Professor of Pathology, Medical College, Calcutta.

THE frequent great difficulty in finding malarial parasites in advanced cases of chronic malaria, and the failure of quinine to influence some such cases has caused doubt to be thrown on this stage of the disease being purely malarial. Thus, Ross, in his preliminary survey of the question of *kala-azar*, wrote: "Lastly, as Manson has lately suggested to me, and as I have often thought in respect to some cases of paludism, we may, in such instances as occur in *kala-azar*, have an auxiliary bacterial invasion of the liver and spleen following the primary protozoal infection by the parasites of malaria." In the same report he discusses the low secondary fever, *la fèbre symptomatique* of Kelsch and Kiener—which is not affected by quinine and accompanies the greatly enlarged and congested livers and spleens of this stage of the disease. More recently still Stephens and Christophers in a paper on

"Malarial fever without parasites in the peripheral blood" at the Nagpur Malarial Conference, referred to the fact that they had very frequently been unable to find parasites in "so-called Malarial cachexia and enlarged spleen," and questioned whether these cases were purely malarial in nature. In the discussion on this paper I referred to my experience in Assam, to the effect that although at any given examination parasites are very frequently absent, yet by following up cases for months and repeatedly examining them during marked exacerbations of the fever, parasites can be found in all stages of the disease up to the day before death, as in the case whose chart is given in my report on *kala-azar*, although they may certainly be absent for considerable periods during the low fever. Still more recently the suggestion has been put forward that these chronic cases are Malta Fever; but the absence of serum reactions in a number of such cases and the totally different temperature curve and mortality noted in my paper in last month's issue of this journal entirely negative this theory. The generally observed relationship between the proportion of enlarged spleen and the malariousness of a district has recently been confirmed by the members of the Malaria Commission of the Royal Society, for Captain James, I.M.S., in his paper on "the value of the spleen test as an indication of the prevalence of Malaria," as read at the Nagpur Conference, states: "In children with enlarged spleens, however, parasites are commonly found, and a relationship exists between the enlarged spleen rate of children and the parasite rate of children in any place." This did not, however, hold true of adults, in whom chronically enlarged spleens would affect the results.

The question whether the so-called malarial cachexia is a purely malarious condition, or if there is some secondary cause of fever present in the later stages appears, then, worthy of discussion, and in the event of the former conclusion being arrived at, the frequent failure of quinine to cure these chronic forms of malaria fever requires explanation. As the parasites become more difficult to find as the disease progresses, which is not surprising in the view of the fact that Stephens and Christophers have recently shown that the malarial parasites may be absent for days from the peripheral circulation of acute recent malarial infections in which no quinine has been given, it is evident that we must turn to other evidence of malaria for the elucidation of the problem. One such method is that of the large mononeuclear white corpuscle increase, which these authors regard as diagnostic of malaria, even in the absence of the parasites from the circulating blood, an observation the value of which I have now confirmed in about 100 cases of malarial fever. As long as the paroxysms of fever are malarial in origin this typical leucocyte change should be found during the remissions of the fever, while if a secondary fever of bacilliary origin should supervene the malarial count should soon disappear. Again, in such cases as prove fatal the characteristic black pigment may be sought for in the spleen, liver and other organs, for although the observations of Kelsch and Kiener, Daniels and Ross have shown that this pigment may disappear from the organs in cases of malarial cachexia, which have died of secondary affections, such as pneumonia, dysentery, phthisis, cancrum oris, etc., without having suffered for some time from paroxysms of actual

TABLE I.

Melanotic pigmentation of the organs.

Clinical.						Naked eye changes.						Microscopic changes. Fine black Pigment.					Complications.
						Spleen.			Liver.								
Number.	Caste.	Sex.	Age.	Nourishment.	Duration of fever, in months.	Weight in lbs. and ozs.	Pigmentation.	Fibrosis.	Weight in lbs. and ozs.	Pigmentation.	Small intestine pigmentation.	Spleen.	Liver.	Small intestine.	Small atrophy.	Cultures of spleen.	
1	H	M	14	Bad .	+2	0-10	++	-	2- 4	+	-	++	+	+	-	...	
2	H	M	13	Very bad	$4\frac{3}{4}$	1- 9 2-13	++	+	2-13	-	+	++	+	...	...	...	
3	H	M	24	Do.	$5\frac{3}{4}$	1- 2	+	+	3- 0	-	++	++	+	..	...	...	Cancrum oris.
4	H	M	25	Do.	$+1\frac{3}{4}$	1- 5	++	++	3- 6	+	++	++	++	++	+	...	
5	H	M	60	Do.	+2	12	++	+	2 3	+	-	++	++	+	+	...	
6	H	M	35	Bad ...	$10\frac{3}{4}$	14	+	-	1-11	-	++	+	+	+	++	...	Liver cirrhosed.
7	H	F	35	Do. ...	$3\frac{3}{4}$	12	+	-	2- 2	-	+	+	+	-	++	...	Dysentery and cancrum oris.
8	H	M	12	Very bad	+2	1- 6	++	-	1-12	-	+	++	++	++	+	-	Cancrum oris and pur. meningitis.
9	H	M	25	Do.	...	1-10	+	-	3- 6	+	-	++	++	++	+	-	Œdema of lungs.
10	H	M	50	Bad ...	..	2- 9	++	+	3- 5	+	++	++	++	++	+	...	Necrosis of jaw.
11	H	M	19	Do. ...	6	2- 0	++	-	2- 8	+	++	++	++	...	...	...	Dysentery.
12	M	M	25	.....	$+1\frac{1}{4}$	2- 0	+	-	3- 2	-	+	+	+	..	...	-	
13	H	M	22	Fair .	...	$12\frac{1}{2}$	+ +	+	2-13	-	-	+ +	+ +	...	...	...	
14	H	M	22	Very bad	6	1-10	+	-	2- 2	-	++		...	+	++	-	Dysentery and pneumonia.
15	H	M	22	Do.	$3\frac{1}{2}$	1- 8	+	-	1-12	-	+	...	+	...	...	-	Pneumonia.
16	H	M	11	Fair ...	$+1\frac{1}{3}$	$5\frac{1}{4}$	+	+	1-11	++	++	...	++	++	++	-	Bright's disease.
17	M	M	25	.....	...	2- 2	++	+	...	++	-	...	++	...	...	-	Tubercle of lung, Cirrhosed liver.
18	H	F	18	Very bad	2	3- 0	++	-	2- 8	-	-	++	+	...	...	...	Brain pigmented.
19	M	F	20	Do.	$4\frac{1}{2}$	2-14	+ +	+	3- 7	-	-	+ +	++	..	...	-	Brain pigmented, dysentery.
20	M	M	32	Fair ...	...	3- 0	++	-	3- 4	-	+	++	++	...	...	-	

malarial fever, yet in cases in which active malarial fever has occurred shortly before death such pigment is found in fine granules throughout the liver and spleen, in addition to any coarse granules in the fibrous supporting tissue of these organs as a result of older malarial infection. The presence of these widely distributed fine melanine granules may then be taken as evidence of recent active malaria, and if found in the great majority of cases of fatal malarial cachexia, who have suffered from fever shortly before death, that would be very strong evidence that their recent fever was malarial and not of a secondary nature. Further bacteriological examinations of the spleen, *post-mortem*, will show if there are any organisms constantly or even frequently present which might be the cause of a secondary fever. Observations on these points made by me during the last sixteen months at the Medical College and General Hospitals in Calcutta may, perhaps, throw some light on these questions.

Naked-eye and Microscopical Changes in the Organs, Post-mortem, in Malarial Cachexia.

The data of 20 cases of malarial cachexia successively examined *post-mortem* at the Medical College Hospital, Calcutta, are condensed in Table I. These cases had been diagnosed in the wards as malarial cachexia, while many of them had ultimately died of one or more of the common complications or secondary diseases so frequently met with in these cases, as shown in the last column of the table. Column 5 shows the state of nourishment at the time of death, emaciation being a constant and very characteristic feature of the series. Next the weights of the spleen and liver are given, together with the

naked eye evidence of pigmentation of these organs and of the mucous membrane of the small intestine. Two + + indicate a marked darkening of the organs or tissues, and one + a lesser, but still distinct degree, of the same, while — represents an absence of definite naked eye pigmentation. It will be seen that the spleen always showed darkening, and the small intestine usually also showed it, while, on the other hand, the liver frequently did not show it, the darkening here being often obscured by the contrary effect of coincident fatty change. The columns 12 to 14 give the degree of fine black pigmentation in the same organs seen on microscopical examination of sections as opposed to coarse pigmentation of old malaria, a + sign indicating well-marked fine pigment distributed widely through the organ, which is clear evidence of recent malarial disease, and two + + denoting an extremely marked change of the same nature. A glance at the table shows that this black characteristic malarial pigment, of a fine and widely distributed nature, was present in one or more of the tissues examined in every case diagnosed during life as malarial cachexia. On the other hand, some other cases which showed marked naked eye pigmentation, but in which the patient had died of some totally different disease, such as fracture of the spine, without having suffered from fever for some time, only coarse pigment in the fibrous supporting framework of the spleen and liver was found, and such was also the case in a patient who had died of a combination of diseases, among which a very distinct cirrhosis of the liver of undoubtedly malarial origin had played an important part, producing great ascites. This last condition was also met with in a marked degree in case 6 in

this table, together with fine black pigment of recent origin. The common malarial fibrosis of the spleen was also frequently met with as shown in column 8. It will also be seen that the spleen was markedly or extremely enlarged in all the cases. In many of the cases the spleen and liver also showed other well-known changes of chronic malaria, such as the angioma-like tissue of the cavernous sinuses resulting from absorption of the necrotic areas of the acute disease, and the enlarged regenerated lymph follicles in the spleen; and the zones of angiomatoid tissue and of atrophy, and connective tissue hyperplasia and more or less well-marked chronic peri- and monolobular hepatitis in the liver. There is clear evidence, then, of a chronic malarial process, together with the fine black pigment showing recent actual malarial infection.

In this connection it is interesting to note both how recently before death fever of apparently malarious nature occurred, and its degree and type. For purposes of studying this point I have examined the clinical notes of the cases tabulated, with the following results:—In 10 of the cases given in Table I, the duration of fever before admission was recorded, and the average time was just under four months, the shortest being $1\frac{1}{2}$ and the longest 9 months, while if the average time in hospital before death occurred is included, the total duration of the fever averages just five months, and the periods varied between 2 and 10 months. These figures suffice to show that the series are typical of chronic malarial fever and do not include acute cases. Further, out of the 20 cases, 5 died within one week of admission, 6 more within three weeks, and the remaining 9 between one and two months after admission, most of the cases having been

admitted in a hopelessly cachexial condition. In several instances it is recorded that the patients had suffered from fever for several months before admission but had undergone no treatment for it, while as cases on which *post-mortems* are performed belong only to the poorest, friendless classes, it is certain that very few of them could have had proper medical attendance before coming to hospital. Every case which lived for any length of time after admission to hospital suffered from fever, usually of an irregularly intermittent type, nearly always without typical ague, and generally with a range of temperature between normal or slightly sub-normal to from 100 to 102. This is just the kind of comparatively low fever during which it is very difficult to find malarial parasites in the peripheral circulation, yet we see every case showed the fine pigment uniformly distributed through the liver and spleen, which is characteristic of recent malarial infection, showing that the fever while in hospital was also malarious in its nature, and this was confirmed by the characteristic leucocyte changes of malaria, (to be dealt with further on in this paper) having been found during life in the few cases of Table I which were examined for it.

Pigmented atrophy of the mucous membrane of the small intestine.

In my original report on *Kala-azar* I drew attention to a form of pigmented atrophy of the mucous membrane of the small intestine, accompanied by so great a loss of digestive power that unaltered starch granules could be found in numbers in the fæces, having passed through the whole digestive system intact, and accompanied by a chronic and intractable diarrhœa and very great emaciation. It was not until

about two years later that I was able to make a careful microscopical investigation of the material from a series of cases, but unfortunately after having drawings and photographs made of the sections, the whole was destroyed in a fire. However, I have now been able to examine a second series from cases of malarial cachexia in Calcutta, with the result that I have been able to confirm my earlier results, and furnish another link in the chain of evidence of the identity of all the pathological lesions in the Assam epidemic malarial fever and the chronic forms of malaria so frequently met with in Bengal. By means of examinations of more acutely fatal malarial infections the earlier stages of the changes have also been traced, and I hope to be able to publish drawings of them shortly, and will only here refer briefly to the frequency and importance of these changes, as they do not yet appear to have received the attention which they deserve. A reference to column 11 of Table I will show that in thirteen out of the twenty cases of naked-eye pigmentation of the small intestine was noted, while column 14 reveals the fact that a still larger proportion, namely, nine out of ten cases, in which sections of the small intestine have been cut, fine black pigment was detected in the mucous and submucous coats with the microscope. In cases dying of acute malarial fever only congestion and catarrh without naked-eye pigmentation is usually found, and in such cases fine pigment, together with, in some cases, actual malarial parasites, can be found in the intestinal mucous membrane, accompanied by a marked cellular infiltration of especially the villi and between the tube glands, but without any atrophy of the

epithelial layers. In the chronic cases here dealt with very much more marked changes are seen, often of such a degree as to completely alter the appearance of the mucous membrane and make it scarcely recognisable as such. Thus, in a typical advanced case whole sections of the tissue may show not a single villus or tube gland with well-defined epithelial cells. The villi will be only represented by small stumps composed of fibrous and a few small round cells, while the tube glands will have entirely disappeared and the whole membrane will be thinner than normal, and show much black pigment and fibrous and cellular degeneration. Such a mucous membrane as this can have little or no secretive or absorptive powers, and the great emaciation is thus fully accounted for. Every intermediate degree between the early stage of acute cases and the extreme atrophic condition have been met with in different cases of the present series accompanied by the presence of the typical black malarial pigment in the intestinal mucous membrane, as well as in the spleen and liver of the same cases. I cannot help thinking that this pigmented atrophy of the mucous membrane of the small intestine is the most important feature of this class of cases as far as the fatality of the disease is concerned, for knowing as we do that the digestive process carried on normally in the small intestine is essential to life, it is impossible to examine sections of advanced stages of this form of atrophy without wondering how the patients could have survived as long as they did. In marked cases the naked eye changes are also unmistakeable, for the mucous membrane has a more or less dark slaty appearance, which on

close examination is found to be produced by innumerable very fine black dots closely aggregated together. The change is always most marked in the upper part of the small bowel, although in advanced cases it may extend throughout its whole length, while very rarely it may also be well marked in the mucous membrane of the stomach. The membrane is usually thinner than normal, although not always so. This condition has nothing whatever to do with the bites of anchylostoma, and in every case I have seen, it was associated with evident naked eye malarial pigmentation of the spleen and often also of the liver, a fact which is confirmed by the microscopical examinations of the cases recorded in Table I.

Lastly, this condition is of great importance in connection with the treatment of malarial cachexia, both dietetic and therapeutical. The importance of easily assimilated, or partially digested, foods in such a condition does not require insisting on. Further the chronic intractable diarrhœa of advanced cases of this atrophy is a very fatal symptom in malarial cachexia, and one most difficult to treat, bismuth and salol having given me the best results. This condition is also, I think, of great interest as furnishing an obvious explanation of the frequent failure of quinine given by the mouth, to have any marked controlling effect on chronic malarial fevers, which may nevertheless rapidly yield to the hypodermic use of the drug, a remark which applies to the congested and catarrhal condition in some acute cases of malarial fever, as well as to the atrophic stage in chronic ones, and also furnishes an indication for the earlier and more frequent use of the drug subcutaneously in all cases which resist treatment by the mouth for more than a very few days.

TABLE II.

Leucocyte Variation in Malarial Cachexia.

Number.	Nationality.	Sex.	Age.	White corpuscles.	Polyneuclears.	Lymphocytes.	Large mononeuclears.	Eosinophiles.
1	European	M	29	1,000 per c. m.	58	30	12	...
2	Hindu ...	M	18	2,250 do.	30	52	27	...
3	Eurasian	F	13	5,750	49·6	23·2	26·8	0·4
4	,, ...	F	26	3,750	43·2	32·4	23·6	0·8
5	Hindu ...	F	8	Rather few.	23·0	61·0	16·0	...
6	European	F	11	1,625 per c. m.	32·8	44·0	23·2	...
7	,, ...	M	14	1,250	66·8	27·6	5·2	0·4
8	,, ...	M	5	1,250	43·6	36·0	20·4	...
9	,, ...	M	10	....	52·4	22·46	25·2	...
10	,, ...	M	28	Fairly numerous	21·6	38·10	40·0	0·4
11	,, ...	M	33	Very few	50	28	22	...
12	Negro ...	M	42	....	58·0	18·0	22·8	1·2
13	European	M	16	1,500 per c. m.	38·0	39·2	22·8	0·4
				625	44·0	34·8	21·2	...
14	,, ...	M	28	2,500	57·6	30·8	10·4	1·2
				(6,000	77·0	21·6	2·8	3·6)*
15	,, ..	M	31	1,250	43·6	40·4	16·0	...
		F		(5,000	70·0	22·8	5·2	2·0)*
16	,, ...		...	3,000	36·0	49·2	14·8	...
17	,, ...	M	5	1,500	20·4	56·8	22·8	...
				Average ...	42·5	36·5	20·7	0·3

* No fever for one month.

Kala-azar cases.

1	Native ...	...	...	Few ...	44·0	31·6	24·0	0·4
2	,, ...	...	...	Few ...	40·4	28·8	25·6	5·2
3	,, ...	...	...	Few ...	41·2	27·6	24·8	6·4
4	,, ...	...	...		60·4	9·6	14·0	16·0
5	,, ..	...	...	Few -	35·6	34·0	30·0	0·4
6	,, ...	...	...		44·8	39·2	16·0	...
7	,, ...	..	...	Very few ...	54·8	37·2	18·0	...
8	,, ...	...	...		54·4	31·2	14·4	...
9	,, ...	..	...	Very few ...	57·6	20·8	21·6	...
10	,, ...	...	...		42·0	38·4	19·6	...
				Average...	46·6	29·8	20·8	2·8

The leucocyte changes in Malarial Cachexia and their diagnostic importance.

I have elsewhere[1] dealt with the type and degree of anæmia in chronic forms of malaria as exemplified in the case of the Assam form of the disease known as *kala-azar*, and the fact that the changes met with in that disease are identical with those I have found in chronic forms of malaria in Calcutta, furnishes yet one more proof of the malarious nature of the Assam fever. The later cases of Table II of my recent paper[2] on the leucocyte changes in continued and remittent fevers of India illustrate these changes, so that it is unnecessary to further discuss those points. The leucocyte variations, however, are worthy of closer attention, for in the table just referred to, it is evident that the large mononeuclear increase accompanying a low total leucocyte count, is found in the chronic anæmic cases of malarial fever as well as in the acute ones, and these changes may, therefore, be used as a test of the malariousness, or otherwise, of a series of malarial cachexia cases. Such a series is given in Table II, the first 17 cases being a consecutive series of malarial cachexia cases examined in Calcutta, while the last ten are a consecutive series of the Assam malarial fever (*kala-azar*), half of which were made from slides, kindly sent me by Dr. Bentley (before his recent "discoveries") and the latter by Dr. Dodds Price, of the Nowgong district. The similarity of the counts in each series is evident at a glance, and a brief study of them will be sufficient to prove conclusively that both series show the typical variations peculiar to

[1] *Journal of Pathology and Bacteriology*, 1898.
[2] *British Medical Journal*, 5th April 1902.

malarial fevers. The cases had all suffered from a recent fever, usually of a low intermittent kind, but in some of them of a remittent type, with the exception of the second examination in cases 14 and 15, which were made when the patients had been free from fever for one month. These latter serve to prove that when malarious subjects have had no fever for some time the differential leucocyte count reverts to the normal, and at the same time the total number of leucocytes rise so as to approach the normal proportion. It is evident, then, that any cases of malarial cachexia which have been free from true malarial fever for any length of time will no longer show the typical large mononeuclear increase, accompanied in chronic cases by a decrease of the polyneuclear, and an increase in the lymphocytes. These changes, however, are seen to be have been very constantly present in the cases tabulated, with the exception of case 7 of the Calcutta series, which happened to be examined at a time when the temperature was on the rise, at which period the large mononeuclear increase may not be found, especially in cases with a very low total leucocyte count. There is clear evidence, then, that even the comparatively low and irregularly intermittent fever of most of these chronic cases was still of a malarial nature. In this connection case 13 is of great interest, in contrast with Nos. 14 and 15, for, unlike the latter, his fever continued for several months of an intermittent and occasionally remittent type, not stopped by quinine, and yet at both examinations at an interval of $2\frac{3}{4}$ months a very well-marked malarial large mononeuclear increase of over 20 per cent. was found. If in this and the other chronic cases a secondary fever of non-

malaria origin had ensued, an alteration in the leucocyte count might have been expected, for I have been fortunate enough to have made counts in cases of malaria before the onset of such secondary complications as phthisis, dysentery, pneumonia and liver abscess in different cases, and with the onset of each of these affections the typical malarial counts disappeared, and those of the different complicating diseases appeared. If, then, there is any secondary infection in these chronic cases of malaria which accounts for the low fever with very few or no parasites in the peripheral circulation it must both produce the typical leucocyte changes of malaria and also the widely distributed fine pigmentation of the internal organs, but until some disease other than malaria is discovered which will do this, we may safely conclude that the cases of malarial cachexia dealt with in this paper were from first to last entirely of malarial origin.

In further support of this view it may be mentioned that bacteriological examinations have been made of the spleens of 11 of the cases given in Table I, with negative results, thus confirming the earlier observations of Giles and myself in cases of the Assam epidemic malarial fever, although it must be borne in mind that it has been recently shown that the internal organs are not always sterile in healthy animals immediately after death, and I have myself obtained cocci from the spleen in other cases from quite warm bodies, so that the occasional finding of such organisms in this organ after death cannot be accepted as evidence of a secondary infection unless met with fairly constantly and in large numbers.

A reference to the average number of the different forms of white corpuscles in the Calcutta

and in the Assam series given in Table II is sufficient to prove that both series show typical malarial changes. The large mononeuclear in each having averaged just over 20 per cent., thus furnishing the final proof that *kala-azar* is also of purely malarial origin from first to last, for many of these cases were in the later stages of the disease, and I have made counts of a still larger number which show precisely similar changes.

Relationship of total leucocyte decrease to the failure of quinine in malarial cachexia.

One more point remains for consideration, namely, the frequent failure of quinine to influence the fever in very chronic cases of malaria. I have pointed out above the importance of the pigmented intestinal atrophy in preventing the absorption of the drug, but this will not explain all the facts, for, as I mentioned in my report on *kala-azar*, it may also fail in some cases when given hypodermically, a fact which I have confirmed more than once recently. In the report referred to, I suggested that this failure might be related to the very great decrease in the total number of leucocytes in these chronic cases of malarial fever, and recent experience has very strongly confirmed this view. Column 5 of Table II shows that the leucocytes are nearly always markedly, and often extremely, reduced in these cases. This can be easily detected with practice in a blood slide, and can be roughly gauged by the time it takes to count a given number of leucocytes in a well-spread stained smear. In Table II "fairly numerous" means that the white corpuscles were somewhere about the normal or only slightly reduced; "few" means that they

were markedly reduced, and "very few" that they were very scanty indeed, some difficulty being found in counting 250 in a slide, the number counted in all the cases tabulated except those in which no decimal figures are given in which only 100 could be enumerated. But not only are the total numbers decreased, but the important phagocytitic polyneuclears are also relatively much fewer than normal, in proportion to the increase of the small and large mononeuclears, so that the total number of polyneuclears per cubic millimetre is disproportionally decreased. Now, I find that it is just in those cases in which these changes are most marked, that quinine, even hypodermically, most conspicuously fails in cases which show the typical mononeuclear increase and pigmentations of recent active malaria. Case 13 in Table II is a very good illustrative example of this important fact. The first time he was examined only 1,500 leucocytes per cubic millimetre were found, and 38 per cent. of these were polyneuclears. In spite of full doses of quinine by the mouth the fever continued steadily, and after $2\frac{3}{4}$ months had past, the leucocytes were found to number only 625 per cubic millimetre, or less than one-tenth of the normal, while the proportion of polyneuclears was little more than half the normal, their total numbers being thus only about one-twentieth of the normal. At this time quinine, hypodermically, did have some effect in lowering the range of the fever, but it failed to stop it. During the same period of time there had been a slight improvement in both the hæmoglobin and red corpuscles, so that the continued decrease in the number of the leucocytes and the persistence of the malarial differential count were

the only signs the blood showed of the progress of the disease, parasites not having been found in the two slides examined. The extreme absolute reduction of the polyneuclear white corpuscles is, then, the most characteristic feature of those cases of chronic malarial fever, which resist treatment with quinine, and I would suggest the following hypothesis to account for the fact. It is well known that this drug acts most efficiently at the time the young spore forms are free in the blood, possibly by killing them outright. It is, however, equally possible, and perhaps more probable, that many of the young forms free in the blood are only so far affected by the quinine as to suffer partial paralysis of the power of movement whereby they make their way into the comparatively safe haven of the interior of the red-blood corpuscles, and that this gives the phagocytic leucocytes a much more favourable as well as longer opportunity of englobing and destroying them. If, however, the polyneuclear white corpuscles are so many times fewer than normal, as is the case in these very chronic forms of malarial fever, there will not be enough of them to take full advantage of the paralysing influence of the quinine on the free spore forms of the parasites, and those which are not killed outright by the quinine drug, are thus enabled to make good their escape into the red cells, and multiply once more. The very fact that the phagocytes, become so greatly reduced in chronic forms of malarial fever, strongly suggests a persistent fight between them and the parasites, while the latter being much the smaller and less developed bodies, would naturally be most injuriously infected by quinine in the minute doses in which it reaches the blood.

If this is so, then our efforts should be directed to increasing the white corpuscles and especially the polyneuclears at the same time that quinine is given hypodermically. The great decrease of the polyneuclears will also account for the frequency with which malarial cachexia cases succumb to the invasion of the organisms of such terminal affections as pneumonia, cancrum oris, dysentery and phthisis.

The method and application of the differential Leucocyte Count.

In conclusion I will take this opportunity to add a few lines on the method of the differential leucocyte count, as I frequently get letters asking for guidance on this point, while I am so convinced of its great value as a simple and rapid method of diagnosis between malarial and other fevers of the tropics, that I have come to regard the search for malarial parasites, at any rate in cases which have already been dosed with quinine, as almost a waste of time as a purely diagnostic measure in ordinary clinical work. For purposes of the leucocyte count thin blood smears should be prepared by placing a small drop on a slide, which has been carefully cleaned with alcohol and dried, and then placing a needle flat on it across the slide, and as soon as the blood has run out along it for a short distance, but not as far as the edge of the glass, the needle is made to glide down the length of the slide, so as to spread the drop out in a long smear. It is now fixed for about half an hour in absolute alcohol, being placed in a bottle of it, which can be used for a long time, and is then ready for staining. The best results for both the search for parasites and the corpuscle count can be obtained by the use of Romanosky's stain,

but it has the disadvantage of being difficult to prepare and in being unstable so that it is liable to suddenly fail, and consequently is not very convenient except for use in a well-equipped laboratory. A more reliable and very effective and convenient stain for both parasites and leucocytes is hœmatin made up as follows. Hæmatin, 2 grammes, is dissolved in 50 c. c. of absolute alcohol, and this solution subsequently added to 1,000 c. c. of a saturated solution of potash alum (50 grammes in 1,000 c. c.). This solution may be kept in a bottle, and the fixed slides placed in it for half an hour and then well washed. If it is desired to specially bring out the eosinophile corpuscles, as in a slide from a case of anæmia suspected to be caused by anchylostomiasis (in which this form may number from 5 to 30 per cent.), then after staining with hæmatin, a weak solution of eosin in water may be run over the slide. In counting, 250 corpuscles should be enumerated, unless they are too scanty for this number to be found, which I have never seen in a good smear except in some chronic malarial cases. In counting it is best to begin at one edge a little way from either end and to work backwards and forwards across the slide, as a larger proportion of polyneuclears will be found near the edge and of lymphocytes in the central portions. In this way I have in several instances found that two different counts of separate portions of the same slide of from 250 to 500 corpuscles did not show a variation of as much as one per cent. of either kind. The only remaining difficulty is the discrimination between the lymphocytes and the large mononeuclears, the tendency at first being to include too large a proportion in the last category. Personally I always take advantage of the fact

that the average size of the large mononeuclears, as given by Cabot, is almost the same as that of the polyneuclears, and therefore only count as large mononeuclears those single neucleated white corpuscles which are as large as, or larger, than the average polyneuclear, and this gives a more easily followed line of division between them and the lymphocytes than any other arbitrary standard. It is well to begin with counting normal blood slides until fairly accurate counts are uniformly obtained. The polyneuclears vary normally between 62 and 75 per cent., the lymphocytes between 15 and 30, and the large mononeuclears between 3 and 8 per cent., to take the widest limits given by different authorities. In a leucocytosis, such as in lobar pneumonia, suppurative conditions, including liver abcess, cerebro-spinal fever and cholera for example, the proportion of polyneuclears is increased to 80 to 95 per cent. In malarial fevers and typhoid, on the other hand, the total number of leucocytes is decreased, except when the latter is complicated by hæmorrhage, peritonitis or pneumonia, when an increase may occur. As I have shown elsewhere, however, the counts in these two common forms of continued and remittent fevers differ from each other, for in malaria the large mononeuclear corpuscles are markedly increased during the remissions of the fever from 12 to 30 or rarely even 40 per cent., without any marked increase of the lymphocytes, except in chronic cases, while in typhoid it is the lymphocytes that show a marked increase, except in some of the most severe cases which present no clinical difficulties in diagnosis,—while the large mononeuclears are not increased above the normal limit of 8 per cent. except in very late stages

of the disease in a few cases, and then not before the fourth week or during convalescence in my experience, when they may reach 10 to 12 per cent. The increase of the lymphocytes in typhoid fever may be found well marked, that is they may number about 40 per cent. as early as the beginning of the second week of the fever, while I have frequently been able to diagnose typhoid by this change when the vital reaction was still absent, and to confirm my opinion by obtaining a typical reaction at a later date. Since my original paper on the subject was written I have completed counts and serum tests in upwards of 200 cases of fever, of which I also have short-hand notes and charts which I hope to analyse shortly and am more than ever convinced of the value of the differential leucocyte counts in diagnosing between typhoid and malarial remittent fevers or in excluding both these and pointing to some other cause for the fever, and this is specially true of the chronic malarial fevers treated of in this paper in which parasites are so scanty and difficult to find. The best time to make the blood slides is in the morning before a full meal has been taken, as the temperature is usually lowest in malarial cases at this time, and consequently the large mononeuclear increase is best marked, while disturbances due to the active digestion are avoided. More than one examination is sometimes necessary in order to clear up a doubtful case.